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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,830	12/05/2003	Florian Von Der Mulbe	22122-00009-US	8653

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CONNOLLY BOVE LODGE & HUTZ LLP
1875 EYE STREET, N.W.
SUITE 1100
WASHINGTON, DC 20036

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,830	VON DER MULBE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-23 and 29-34* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-16 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/28/2008 has been entered.

Currently, claims 1, 4, 6-23 and 29-34 are pending.

Any rejections and objections not reiterated in this action have been withdrawn.

Election/Restrictions

Applicant elected Group I with traverse in the reply filed on 7/1/2005.

Claims 17-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/1/2005.

Currently, claims 1, 4, 6-16 and 29-34 are under consideration.

Response to Arguments - 35 USC § 112

Applicant's arguments, see pages 3-8, filed 1/28/2008, with respect to the rejection of claims 1, 4, 6-16 and 29-34 under 35 U.S.C. 112, first paragraph, have been fully considered and are persuasive. The previous rejection of claims 1, 4, 6-16 and 29-34 has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6-9, 11-16 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent No. 5,580,859, cited in a prior action; see the entire reference) in view of Chen et al (WO 99/20774, cited in a prior action; see the entire reference) and Fomsgaard (WO 00/29561 A2; see the entire reference). This is a new rejection.

Felgner et al teach pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a modified mRNA that encodes a polypeptide, wherein the modified mRNA and wild type mRNA encode a polypeptide having an identical amino acid sequence (e.g. column 4, lines 32-45; column 5, lines 7-20; column 8, lines 28-29). Modifications taught by Felgner et al include capping the mRNA, circularizing the mRNA, or chemically blocking the 5'

end of the mRNA (e.g. column 9, lines 14-27). Felgner et al teach pharmaceutical compositions, wherein the modified mRNA comprises a 5' cap structure or a 5' untranslated sequence that does not require a 5' cap for translation (i.e. an internal ribosomal entry site, IRES) (e.g. column 11, lines 35-63; column 24, lines 30-67; column 25, lines 1-36). Felgner et al teach pharmaceutical compositions, wherein the modified mRNA comprises at least one analogue of a naturally occurring nucleotide such as an amino-7-dUTP nucleotide to block the 5' or 3' end from RNase (e.g. column 12, lines 15-30). These modifications of the mRNA retard degradation of the mRNA in the cell (e.g. column 9, lines 15-27). Further, the mRNA is preferred because it does not self-replicate, does not integrate into the genome, and allows transient expression of a gene product (e.g. column 6, line 38, to column 8, line 35). Felgner et al teach pharmaceutical compositions comprising modified mRNA molecules encoding growth hormone, cytokines (e.g. interleukins and interferons), tumor antigens, viral antigens or pathogen antigens (e.g. column 21, lines 56-67; column 22, lines 1-15). These proteins have multiple antigenic epitopes (polyepitopes). Felgner et al teach that is advantageous to further include a cytokine in the form of a polypeptide or polynucleotide (e.g. column 8, lines 35-41). Felgner et al teach pharmaceutical compositions further comprising a cytokine in the form of an mRNA or polypeptide (e.g. paragraph bridging columns 22-23; column 8, lines 35-40).

Felgner et al do not teach the composition where the mRNA has (i) increased GC content relative to that of a wild type mRNA encoding the polypeptide, (ii) maximum GC content, (iii) substitution of all rare codons with codons recognized by abundant cellular tRNAs, and (iv) no 3' untranslated AU-rich sequences.

Chen et al teach a vaccine comprising a modified MSP-1 nucleic acid sequence with the following features: (i) increased GC content, which was produced by lowering the overall AT content, (ii) absence of all mRNA instability motifs, (iii) replacement of all rare codons with preferred codons of mammary gland tissue, and (iv) replacement of codons with codons that code for the same amino acids as the wild type codons (e.g. page 3; page 7; page 10, lines 1-13). Chen et al specifically teach that the AUUUA sequence is a recognized mRNA degradation sequence from the 3' untranslated region of GM-CSF mRNA and that this instability sequence should be removed from the MSP-1 nucleic acid sequence (e.g., paragraph bridging pages 7-8). Chen et al teach a modified MSP-1 nucleic acid that has a G/C content increased at least 15% relative to that of wild type mRNA encoding the MSP-1 polypeptide (e.g. SEQ ID NO: 1, 45.5% GC; SEQ ID NO: 2, 24.2% GC). MSP-1 is an antigen that is expressed during the life cycle of the protozoan *P. falciparum* (e.g. page 1, lines 25-34). Chen et al teach that these modifications result in improved expression of the antigenic protein (e.g., page 6, lines 9-23).

Fomsgaard teaches that it was known in the art that rare codons cause pausing of the ribosome, which leads to a failure in completing the nascent polypeptide chain and an uncoupling of transcription and translation (e.g., page 1, lines 30-32). Pausing of the ribosome is thought to lead to exposure of the 3' end of the mRNA to cellular ribonucleases (e.g., page 1, lines 32-33). Fomsgaard teaches that it has been shown that an exchange of the H IV codon usage to that of highly expressed mammalian genes greatly improves the expression in mammalian cell lines (e.g., page 1, lines 27-29). Fomsgaard teaches the construction of a second nucleotide sequence based on a first nucleotide sequence, where the same amino acid sequence encoded by the first and second nucleotide, and the second sequence is designed using the most

frequent codons from highly expressed proteins in mammals, which are shown in Figure 1.

Figure 1 shows the following:

Amino acid	One letter amino acid code	Three letter amino acid code	Codon
Alanine	A	Ala	GCC
Arginine	R	Arg	CGC
Aspargine	N	Asn	AAC
Aspartic acid	D	Asp	GAC
Cysteine	C	Cys	TGC
Glutamine	Q	Gln	CAG
Glutamic acid	E	Glu	GAG
Glycine	G	Gly	GGC
Histidine	H	His	CAC
Isoleucine	I	Ile	ATC
Leucine	L	Leu	CTG
Lysine	K	Lys	AAG
Proline	P	Pro	CCC
Phenylalanine	F	Phe	TTC
Serine	S	Ser	AGC
Threonine	T	Thr	ACC
Tyrosine	Y	Tyr	TAC
Valine	V	Val	GTG

Comparing the preferred codons to all possible codons disclosed in Figure 7 (shown below), it is clear that the preferred codon for each amino acid has maximal GC content as compared to all possible codons for the same amino acid.

aa	Σ	codons
A	Ala	GCX	GCT GCC GCG GCA
C	Cys	TGY	TGT TGC
D	Asp	GAY	GAT GAC
E	Glu	GAR	GAG GAA
F	Phe	TTY	TTT TTC
G	Gly	GGX	GGT GGC GGG GGA
H	His	CAY	CAT CAC
I	Ile	ATH	ATT ATC ATA
K	Lys	AAR	AAG AAA
L	Leu	YTX	TTG TTA CTT CTC CTG CTA
M	Met	ATG	ATG
N	Asn	AAY	AAT AAC
P	Pro	CCX	CCT CCC CCG CCA
Q	Gln	CAR	CAG CAA
R	Arg	MGX	CGT CGC CGG CGA AGG AGA
S	Ser	WSX	TCT TCC TCG TCA AGT AGC
T	Thr	ACX	ACT ACC ACG ACA
V	Val	GTX	GTT GTC GTG GTA
W	Trp	TGG	TGG
Y	Tyr	TAY	TAT TAC

Thus, when all codons are replaced with preferred codons, the coding sequence has maximal GC content while encoding the same polypeptide sequence as the starting nucleic acid sequence.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the mRNA vaccine compositions encoding an antigenic protein of Felgner et al to include the modifications taught by Chen et al, including increasing the GC content, eliminating the 3' untranslated AUUUA destabilization elements, and substituting rare codons with codons recognized by abundant cellular tRNAs, because Chen et al teach it is within the ordinary skill in the art to use such modifications to a nucleic acid encoding an antigenic protein. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace all codons with the preferred codons taught by Fomsgaard, because Felgner et al, Chen et al, and Fomsgaard teach modified nucleic acid sequence.

One would have been motivated to make such a modification in order to receive the expected benefit of increasing the expression of the antigenic protein as taught by Chen et al and Fomsgaard. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent No. 5,580,859, cited in a prior action; see the entire reference) in view of Chen et al (WO 99/20774, cited in a prior action; see the entire reference) and Fomsgaard (WO 00/29561 A2; see the entire reference) as applied to claims 1, 4, 6-9, 11-16 and 29-34 above, and further in view of

Ueda et al (Nucleic Acids Research, Vol. 19, No. 3, pages 547-552, 1991, cited in a prior action; see the entire reference).

The combined teachings of Felgner et al, Chen et al, and Fomsgaard are described above and applied as before.

Felgner et al, Chen et al, and Fomsgaard do not teach a modified mRNA comprising at least one analogue of a naturally occurring nucleotide, where the analogue is a phosphorothioate.

Ueda et al teach mRNA molecules comprising phosphorothioate nucleotide analogs (e.g. pages 548-549, Enzymatic synthesis of phosphorothioate-containing RNAs, and Analysis of the phosphorothioates incorporated into RNAs). Ueda et al teach that mRNA comprising phosphorothioate ribonucleotides is more stable in *in vitro* translation systems (e.g. pages 549-550, Stability of phosphorothioate RNAs). Further, Ueda et al teach that more protein can be synthesized from a phosphorothioate-modified mRNA (e.g. page 551, right column, 3rd and 4th paragraphs).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include a phosphorothioate nucleotide analog of Ueda et al in the modified mRNA of Felgner et al, Chen et al, and Fomsgaard because Ueda et al teach it is within the ordinary skill in the art to use phosphorothioates in mRNA molecules and Felgner et al, Chen et al and Fomsgaard teach modified mRNA molecules.

One would have been motivated to make such a modification in order to receive the expected benefit of increased stability of the mRNA as taught by Ueda et al. Further, one would have been motivated to make such a modification in order to receive the expected benefit of increasing the amount of the translation product as taught by Ueda et al. Based upon the

teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

Applicant's arguments filed 1/27/2006 have been fully considered as they apply to the new rejections presented above but they are not persuasive.

At page 17, the response asserts that neither one of Chen et al and Felgner et al teach a modified mRNA or modified nucleic acid sequence having a maximum GC content.

The response asserts that Chen is not broadly directed to a modified mRNA or a modified nucleic acid sequence comprising a modified nucleic acid sequence comprising a maximum GC content as presently claimed. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the teachings of Felgner et al are broadly directed to a modified mRNA.

Further, the response asserts that lowering overall AT content is not equivalent to achieving a modified mRNA or nucleic acid sequence having a maximum GC content. The response asserts that the teachings of the Chen et al reference are limited to improving expression of MSP-1 in mammary tissue, and that these modifications are directed to embodiments where AT content may increased. This is not found persuasive. Chen et al specifically teach lowering AT content of the sequence (e.g., page 10, lines 1-13). Furthermore,

Chen et al and Fomsgaard teach that it is desirable to replace codons recognized by a rare cellular tRNA with codons recognized by abundant cellular tRNAs. When one replaces all codons with commonly used codons, as taught by Fomsgaard, each codon is maximized for GC content while still coding for the same amino acid (e.g., Fomsgaard, Figures 1 and 7). Thus, the combined teachings of Felgner et al, Chen et al and Fomsgaard would not result in an increase in AT content. Rather, the combined teachings result in maximum GC content.

The response asserts that Felgner et al do not teach a modified mRNA or nucleic acid sequence having altered or maximized GC content and is silent with respect to a modified mRNA or nucleic acid sequences that comprises a substitution wherein at least one codon recognized by a rare cellular tRNA is replaced by a codon recognized by an abundant cellular tRNA. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, these deficiencies are remedied by Chen et al and Fomsgaard.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636